DEPARTMENT OF HEALTH AND HUMAN SERVICES

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National Institute of Allergy and Infectious Diseases

STATUS OF NIH-SPONSORED BASIC AND CLINICAL RESEARCH ON TRANSPLANTATION

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EXECUTIVE SUMMARY

This report, *Status of NIH-Sponsored Basic and Clinical Research on Transplantation,* summarizes the research activities supported by the National Institutes of Health (NIH) and highlights opportunities to further extend transplantation for treatment of an even wider range of diseases. Ten NIH Institutes and Centers support transplantation research with a fiscal year 1999 investment of more than $260 million. Current research programs encompass a broad range of basic, pre-clinical and clinical endeavors and many organs and tissues. This report is organized in three major sections:

1. Introduction, outlining the historical and modern uses of transplantation, barriers to transplantation, and costs of transplantation
2. NIH programs and achievements
3. Opportunities to improve transplantation and to extend its use for the treatment of many diseases.

1. Introduction

History: The principal goal of transplantation is the physical and functional replacement of failing organs and tissues. However, the most striking advances in transplantation have come only in the past 30 years, with improvements in surgical techniques and the development of methods to suppress the recipient's immune responses against the graft. These advancements have made transplantation the preferred treatment for many devastating diseases, including failure of the kidneys, heart, liver, lungs, and pancreas.

Transplantation Today: Today, transplantation procedures are performed using more than 25 different organs and tissues, with first-year graft survival rates often exceeding 80 percent. More than 21,000 solid organ transplants were performed in 1998, an increase of 66 percent since 1988. Kidney transplants accounted for more than half of the solid organ transplants performed in 1998. Also in 1998, more than 45,000 bone marrow transplants were performed worldwide for the treatment of cancer and blood disorders - more than 20,000 of those in the United States.

Barriers to Transplantation: There are two major impediments to transplantation: immune-mediated graft rejection and the critical shortage of organ and bone marrow donors. Progress in organ and tissue preservation and surgical techniques has largely conquered the technical obstacles to engraftment. The primary reason for graft failure is, at present, the recipient's vigorous immune response to the graft. Improvements in immunosuppressive therapy have dramatically reduced acute rejection and increased graft survival for all organs during the first year after transplantation. However, long-term graft survival has not improved significantly in the past two decades due to chronic graft rejection. The mechanisms of chronic rejection differ from those of acute rejection and are less well understood.

The waiting lists for solid organ transplants has quadrupled since 1988 to over 68,000 patients. At the same time, the number of donated organs has increased by only 70 percent to 10,073, with living donation increasing 118% in the last 5 years. In 1998, 4,855 individuals died while on waiting lists, an average of 13 per day. As the American population ages and life expectancy increases, the number and types of transplantation procedures will also increase, putting an even greater strain on the supply of donated organs.

2. NIH Programs and Achievements

The NIH investment in transplantation research has nearly tripled in the past decade. Ongoing efforts are focused on:

- Increasing organ donation and assessing clinical outcomes;
- Developing new reagents and methodologies for histocompatibility testing in minorities;
- Improving immunosuppressive therapies and developing novel approaches to induce immune tolerance; and
- Supporting basic and clinical research targeted to specific diseases, organs and tissues.

Increasing Organ Donation and Assessing Clinical Outcomes: Successful transplantation depends on the availability of donated organs and accurate methods to match donors and recipients. Many public and private efforts are focused on a variety of strategies to educate and encourage donation in diverse populations and settings. Notable among these efforts are:

- **The Secretary's National Organ and Tissue Donation Initiative**: A Department-wide initiative, begun in 1997, to expand the involvement of Federal agencies, including NIH, in efforts to increase donation.
- **Community-based Educational and Behavioral Interventions:** NIH supports a variety of research projects to develop effective interventions to increase knowledge of and willingness to donate, with a particular focus on minority populations.
- **Registries:** NIH supports various registries to facilitate donor-recipient matching and assessments of clinical outcomes. Examples include: The International Bone Marrow Transplant Registry; the Autologous Blood and Marrow Transplant Registry; the Post-Transplant Tumor Registry; and the Louisiana Organ Procurement Donor Registry Program.

Developing New Reagents and Methodologies for Histocompatibility Testing in Minorities: Two decades of NIH support for research to improve donor-recipient matching in minority populations has led to substantial improvements in the number of minorities able to receive a transplant and in graft survival. Populations of particular focus include African-Americans, Hispanics and Alaska Natives. In addition, NIH supports the International Histocompatibility Working Group (IHWG) to standardize and improve histocompatibility testing worldwide through the discovery, development, and distribution of information and new tissue typing reagents. These efforts have helped to ensure that patients will receive the best-matched donor organs available. Future efforts of the Working Group will focus on development of more sensitive and accurate DNA-based, as opposed to serological, technologies for histocompatibility matching. Other activities of the IHWG focus on

expanding knowledge of the role of HLA genes in cancer and autoimmune diseases; understanding HLA diversity in ethnically distinct populations; and establishing the importance of non-HLA genes in graft rejection.

Improving Immunosuppressive Therapies and Developing Novel Approaches to Induce Immune Tolerance: Years of highly productive and intensive basic research has provided the foundation for the development of improved therapies to treat and prevent graft rejection. In the future, enhanced understanding of the human immune system will provide the basis for new therapeutic approaches that do not rely on global immunosuppression. A particularly promising area is the induction of donor-specific immune tolerance, a selective blockade of immune responses directed against the graft. Successful induction of immune tolerance would enable long-term graft survival without the complications and risks of current treatments (e.g., infection, malignancy, and atherosclerosis). NIH is supporting basic, pre-clinical and clinical research to advance the field of immune tolerance through a variety of solicited research programs. These include:

- **The Immune Tolerance Network:** A consortium of 40 institutions dedicated to clinical research of tolerance induction strategies in four clinical areas: kidney transplantation, islet transplantation for type 1 diabetes, autoimmune diseases, and asthma and allergic diseases.
- **Cooperative Clinical Trials in Adult and Pediatric Kidney Transplantation:** Consortia of investigators focused on developing more effective immunosuppressive and tolerogenic treatments to treat and prevent graft rejection.
- **Non-Human Primate Transplant Tolerance Study Group:** A collaborative research program to evaluate novel tolerance induction treatment regimens in kidney and islet transplantation and provide the foundation for clinical applications.
- **NIH Intramural Kidney and Islet Transplantation Program:** A collaboration of researchers focused on clinical trials and non-human primate studies in kidney, kidney-pancreas, and islet transplantation.
- **Autoimmunity Centers of Excellence:** A cooperative group involved in evaluating novel therapies for autoimmune diseases (e.g., type 1 diabetes, rheumatoid arthritis, multiple sclerosis, systemic lupus erythematosus, and inflammatory bowel disease).
- **Innovative Grants on Immune Tolerance:** This initiative will support novel basic research aimed at identifying new tolerogenic targets for future pre-clinical and clinical development.

Organ-Specific Research: NIH support a broad spectrum of research focused on the transplantation of specific organs, including kidney, liver, pancreas, heart, and lung. These efforts focus on: (1) improving organ preservation methods; (2) developing approaches to harvest and expand transplantable cells and tissues *ex vivo*; (3) improving methods for post-transplant monitoring, assessing disease activity, and predicting acute rejection prior to organ damage; and (4) developing more effective approaches to prevent recurrence of underlying disease.

3. **Opportunities in Transplantation**

In the 21st century, there will be many opportunities to extend transplantation to treat a wider range of diseases. NIH is committed to developing new approaches to prevent graft rejection and expand knowledge of the mechanisms of immune rejection. Some of the most promising opportunities include:

- Novel strategies to induce immune tolerance;
- New technologies for early diagnosis and prediction of rejection;
- Use of transplanted cells and tissues to treat neurological disorders such as Parkinson's Disease and spinal cord injury;
- The clinical application of stem cell technologies to a wide range of disorders, e.g., improvements in bone marrow transplantation for cancer and autoimmune diseases, and to replace or assist failing organs;
- The clinical application of tissue bioengineering techniques, potentially in combination with stem cell technologies, to generate artificial organs for transplantation; and
- The development of appropriate ethical standards for the design, conduct and monitoring of transplantation research.

Transplantation is among the most successful and promising areas of medicine. With a wealth of ongoing and planned activities, NIH is poised to continue its leadership role in meeting the challenges of the future.

I. INTRODUCTION

At the threshold of the 21st century, the field of transplantation can reflect on its vast accomplishments. Advancements in transplantation have enabled the replacement of failed organs, the immunotherapy of cancer, and the treatment of genetic disorders. Yet despite these successes, transplantation faces many challenges, including: improving long-term graft survival and function, terminating harsh therapeutic regimens, and reducing lengthy waiting lists for organ procurement. The National Institutes of Health is committed to meeting these challenges and exploring new frontiers in transplantation. In the next century, imaginative new technologies will make it possible for transplantation to treat a wider range of diseases than was thought possible even 10-20 years ago.

SCOPE OF THIS REPORT

This report focuses on basic and clinical transplantation research activities and opportunities that are supported by NIH. Through directed research programs and the wide array of investigator-initiated research, NIH is able to focus the nation's scientific expertise to solve outstanding problems in transplantation. NIH's investment and leadership in research have led to many advancements in transplantation that improve the quality of life for transplant recipients and their families.

Many contemporary topics in transplantation, such as legal and regulatory issues; organ procurement, preservation, and distribution; progress in surgical techniques; approved and experimental therapeutics; and development of medical devices, are elucidated in the Department of Health and Human Services (DHHS) *1999 Report to Congress on the Scientific and Clinical Status of Organ Transplantation*, submitted to the Commerce Committee of the U.S. House of Representatives and the Committee on Health, Education, Labor and Pensions of the Senate. Additionally, the Institute of Medicine's recommendations for organ procurement[1] provide a comprehensive evaluation of DHHS regulations on organ procurement and distribution.

HISTORY

The modern era of organ transplantation began in the late 19th century when new surgical techniques enabled the transfer of organs from donors to recipients. Early transplantation attempts failed, however, and it was not until the early 20th century that the immunological basis of graft rejection was discovered. Furthermore, the widespread clinical application of transplantation has only become possible in the last 30 years with the development of immunosuppressive agents, which inhibit the immune response, thereby reducing organ rejection. Today, transplantation procedures are performed using more than 25 different organs and tissues, with the first-year graft survival rates often exceeding 80 percent. These successes

[1] Institute of Medicine. 1999. *Organ Procurement and Transplantation.* Washington, D.C. National Academy Press.

have enabled physicians to use transplantation more widely in treating a variety of life-threatening and debilitating diseases.

Although the original goal of transplantation was to replace failed organs and tissues, recent advances have made it possible to treat various forms of cancer, metabolic diseases, and immunodeficiencies with transplantation. Society's investment in basic and clinical research has made many of these advances possible. This investment has allowed biomedical researchers to elucidate basic immunological processes and translate them into strategies for improving the success of transplantation.

The immune system, which serves primarily as the body's defense against infection, is also responsible for graft rejection, tumor eradication, and autoimmune diseases such as type 1 diabetes, multiple sclerosis, and rheumatoid arthritis. Transplantation research has led to many landmark discoveries in immunology, including: the human leukocyte antigen (HLA) system, the basis of cellular immunity, and mechanisms of immunological tolerance. These advances have changed the clinical practice of medicine and have greatly enhanced the methods used to diagnose, treat, and vaccinate against a wide variety of diseases. As research continues to expand our understanding of the immune system, our ability to improve the quality of life for transplant patients will also increase.

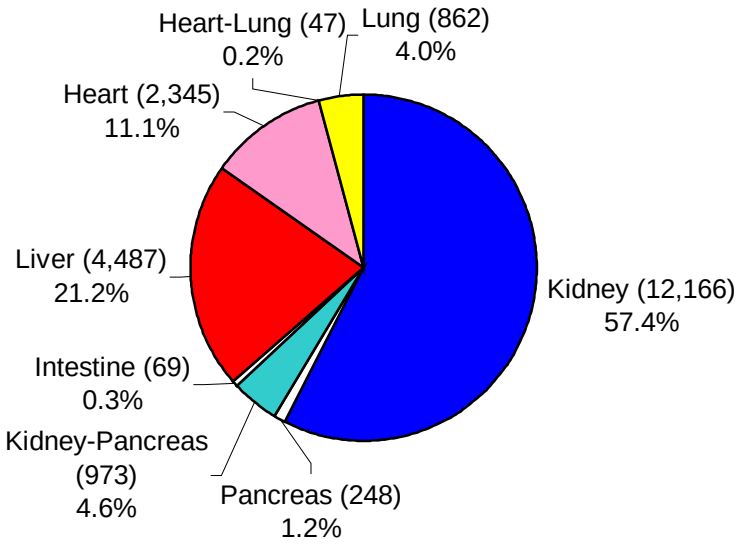
TRANSPLANTATION TODAY

Illnesses such as kidney failure, diabetes, heart and liver disease, and leukemia affect millions of Americans. Without medical intervention, these illnesses almost invariably result in death. In many cases, transplantation of organs, tissues, or cells averts the serious complications of these diseases and is now the preferred treatment.

More than 21,000 solid organ transplantation procedures were performed in 1998 (Figure 1), reflecting an increase of 66% since 1988. This expansion can be directly linked to the development of new and improved immunosuppressive agents that effectively prevent or treat acute rejection. In contrast to one-year graft survival rates, long-term graft survival rates remain relatively unchanged (Table 1). This may be attributed, in large part, to a poor understanding of the cellular and molecular mechanisms of chronic rejection, which lead to long-term graft failure. A failed graft places the patient on the waiting list once again. Because the first graft sensitizes the patient's immune system to a wider range of potential donors, the probability of finding another favorable match is usually low.

Bone marrow transplantation (BMT) is used to treat cancer and blood disorders. In 1998, more than 45,000 BMT procedures were performed worldwide – more than 20,000 of those in the United States. Solid-organ transplantation and BMT procedures are similar in the methods used to match donors to recipients, but unlike solid-organ transplants, in some cases BMT patients may donate their own bone marrow cells.

Figure 1. Solid Organ Transplants in 1998.
Total: 21,197



Percentages and actual numbers, in parentheses, of total organ transplants are shown.

BARRIERS TO TRANSPLANTATION

The two major impediments to transplantation are immune-mediated graft rejection and the critical shortage of organ and bone marrow donors. Graft rejection can be treated with pharmaceutical and biological agents, while addressing problems of organ availability will require improvements in, and wider establishment of, donor registries and the development of alternative organ and tissue sources.

Immune-Mediated Graft Rejection. Progress in organ and tissue preservation and surgical techniques has largely conquered the technical obstacles to engraftment. The primary reason for graft failure is now the recipient's vigorous immune response to the graft. Likewise, the advent of donor-recipient blood group matching has largely eliminated the problem of immediate, or hyperacute rejection. Acute and chronic rejection mechanisms are now the major focus of research in transplantation immunology.

The primary molecular target of the recipient's anti-graft immune response is the human leukocyte antigen (HLA) system. HLA molecules are displayed on the surfaces of virtually all cells, tissues, and organs in the body, and normally serve to alert the immune system to the presence of infectious agents such as bacteria, viruses, and fungi. The genes that encode HLA molecules exhibit tremendous diversity among individuals. This diversity means that a graft from one individual will be recognized as foreign (or incompatible) when transplanted into a recipient who does not share the donor's HLA type. Because each individual possesses several

HLA genes, the chances of achieving an identical match at all the HLA genes are statistically small. Additionally, because the current technology for HLA typing may not detect subtle differences between donor and recipient, "identical" matches between unrelated individuals cannot be guaranteed. Identical twins represent the only perfect match.

T cells of the recipient's immune system initiate acute rejection by recognizing incompatible HLA molecules on the cells of the donor organ. Immunosuppressive drugs prevent acute rejection by inhibiting the activity of such T cells, or destroying them. These therapies, which must be maintained for the life of the graft, have resulted in high 1-year survival rates for every organ (Table 1). The greatest improvement in 1-year survival rates has been for lung and heart-lung transplants, which increased from 42% to 76.3%, and from 51% to 76.7%, respectively, between 1988 and 1996. However, long-term immunosuppression places patients at increased risks of certain infections and malignancies, due to the pivotal role of T cells in controlling these conditions.

Table 1. 1-Year and 5-Year Organ Survival Rates[2].

	Kidney	Liver	Pancreas	Kidney-Pancreas	Heart	Lung	Heart-Lung	Intestine
1 year (%)	89.3	79.2	70.2	89.8	85.5	75.0	76.8	68.6
5 year (%)	66.1	62.0	31.5	68.9	67.7	40.6	42.2	N.A.

Graft versus Host Disease (GVHD). GVHD is a major complication of bone marrow and liver transplantation. Donor T cells, present in the graft, recognize the recipient's normal tissues as foreign, and attack them. Patients develop painful skin and mucous membrane blisters and life-threatening failure of the kidneys, intestines, and liver. HLA-mismatched bone marrow increases the incidence and severity of GVHD. Removal of donor T cells from the graft decreases the incidence of GVHD, but may have unwanted effects such as relapse of disease and lower rates of engraftment.

Organ Shortage. The waiting list for solid organ transplantation has quadrupled since 1988 to over 68,000 patients. The median time spent on the waiting list varies by organ and can exceed two years (Table 2). In 1998, 4,855 individuals died while on waiting lists, an average of 13 per day. The National Institutes of Health (NIH) supports efforts to expand the numbers of potential donors and improve donor registries. However, optimal annual recruitment is estimated at only 15,000[3]. To meet the needs of the tens of thousands on waiting lists, NIH sponsors research into alternative sources of organs and tissues. These alternatives include: stem cell transplantation, xenotransplantation (the use of non-human sources of organs and tissues), *ex-vivo* expansion of cells and tissues, and bioengineering of "artificial organs." Advances in these areas will eventually decrease the reliance on donated organs and, consequently, the time patients spend on

[2] 1998 Annual Report of the U.S. Scientific Registry for Transplant Recipients and the Organ Procurement and Transplantation Network: Transplant Data: 1988-1997. U.S. Department of Health and Human Services, Health Resources and Services Administration, Office of Special Programs, Division of Transplantation, Rockville, MD; UNOS, Richmond, VA.

[3] Institute of Medicine, *Organ Procurement and Transplantation*, National Academy Press, Washington, D.C., 1999, p.46.

waiting lists. However, these studies are in the early stages, and important technical and ethical considerations must be addressed before pre-clinical advances can be brought to the clinic.

For bone marrow transplant recipients, living-related donors are commonly used; about 25% of patients have a suitably matched, related donor. However, at any given time nearly 3,000 patients are searching for a match in the National Marrow Donor Program registry (NMDP), which includes nearly 4 million potential donors. Approximately 90% of Caucasian patients and between 50% and 80% of minority patients find a matched donor. For the remainder, alternate sources, such as mismatched family members and unrelated umbilical cord blood, offer hope for the future.

Table 2. UNOS National Patient Waiting List[4]

	Kidney	Liver	Pancreas	Kidney-Pancreas	Heart	Lung	Heart-Lung	Intestine	Total
Number on waiting list[a]	43,995	14,517	867	1,244	4,135	3,584	233	114	68,689
Median time on waiting list (days)	962	477	281	375	207	567	740	N.A.[b]	

[a] Number of patients on respective organ waiting lists as of December 25, 1999.
[b] Data not available.

COSTS OF TRANSPLANTATION

Costs of organ transplantation procedures vary widely (Tables 3A and 3B) and include: i) pre-transplant evaluation; ii) organ procurement, hospital and physician fees; iii) immunosuppressive medications; and iv) long-term medical follow-up. The wide variability in medical follow-up after the first year, and the lack of complete data for these services, make it difficult to extend estimates past one year. In addition, costs are incurred by medical interventions to delay organ failure or alleviate its symptoms. Not shown in these tables are the costs of corneal transplantation, which, because of lower costs in all categories, are estimated at $8,000 per transplant.

Table 3A. Estimated per-Transplantation and Total First-Year Billed Charges for Solid-Organs (Dollars)[5].

	Kidney	Liver	Pancreas	Kidney-Pancreas	Heart	Lung	Heart-Lung	Intestine
Per Transplant	111,400	244,600	113,700	138,300	303,400	257,700	301,200	473,900
Total (*Millions*)	1,355	1,098	28	134	711	222	14	32

[4] 1998 Annual Report of the U.S. Scientific Registry for Transplant Recipients and the Organ Procurement and Transplantation Network: Transplant Data: 1988-1997. U.S. Department of Health and Human Services, Health Resources and Services Administration, Office of Special Programs, Division of Transplantation, Rockville, MD; UNOS, Richmond, VA.
[5] Hauboldt, Richard A. 1999. Cost Implications of Human Organ and Tissue Transplantations, An Update: 1999. Research Report. Milliman and Robertson, Inc. Note: Billed charges are the only source of costs for many transplants. Actual costs may vary.

Table 3B. Estimated per-Transplantation and Total First-Year Billed Charges for BMT (Dollars)[6].

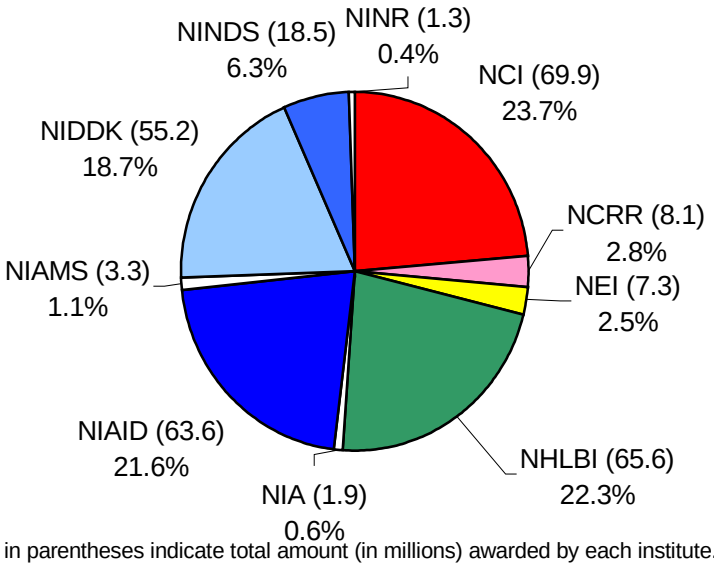
	Bone Marrow Autologous	Bone Marrow Allogeneic Related	Bone Marrow Allogeneic Unrelated
Per Transplant	144,400	232,600	293,100
Total *(Millions)*	1,565	968	496

II. NIH PROGRAMS AND ACHIEVEMENTS IN TRANSPLANTATION

OVERVIEW

NIH is steadfast in its support of basic, pre-clinical, and clinical research in transplantation. Because transplantation is used to treat many different diseases, several institutes enthusiastically support transplantation programs. In FY1999, ten institutes committed more than $260 million to transplantation research (Figure 2), an almost three-fold increase in the last 11 years. The major mechanisms of research support include Interactive Research Project Grants, Program Project Grants, Contracts, and Cooperative Agreements. These support a wide range of projects from basic research in immunology to multi-site clinical trials of novel therapies. Because of the integrative nature of immunology, fundamental discoveries and advances in other clinical disciplines are often applied to transplantation, and vice-versa. NIH transplantation activities and specific achievements therein are summarized in the following sections. In addition, a full listing of NIH's solicited research programs in transplantation is provided in Appendix A.

Figure 2. FY1999 Funding for Transplantation by Institute. Total: $261.3 Million.



Numbers in parentheses indicate total amount (in millions) awarded by each institute.
See Appendix B for the description of institutes.

[6] Ibid.

TRANSPLANTATION RESEARCH COORDINATING COMMITTEE

In April 1989, Congress called for the establishment of a trans-governmental Transplantation Research Coordinating Committee (TRCC), which is chaired by the National Institute of Allergy and Infectious Diseases (NIAID). Each NIH Institute is represented on the TRCC, as well as the Health Care Financing Administration (HCFA), the Health Resources and Services Administration (HRSA), and the Department of Defense (DoD). The TRCC reviews the current and planned transplantation research efforts of each Institute and provides a venue for discussions to coordinate efforts. Periodic reports are developed, published, and distributed that detail the support provided for transplantation immunology by each NIH institute, federal agency, and non-governmental funding organization.

INCREASING ORGAN DONATION AND ASSESSING CLINICAL OUTCOMES

Successful transplantation depends on the availability of donated organs and accurate methods to match donor and recipient HLA types. Subtle HLA differences can go undetected by the current typing methods, yet these differences may be strong enough to trigger graft rejection. Additionally, knowledge of the relevant HLA types in minority populations is incomplete, and may contribute to the lower availability of organs and poorer graft survival in these populations. NIH supports the following efforts to develop organ and bone marrow registries, increase organ donation, and improve HLA typing:

- **Secretary's National Organ & Tissue Donation Initiative.** Vice President Gore and DHHS Secretary Shalala launched this initiative in 1997, with NIAID serving as the lead NIH institute and co-chair for the Initiative's Task Force on Evaluation. Accomplishments include: (i) co-sponsorship of a national conference to evaluate methods of increasing organ donation; (ii) co-sponsorship of a national conference on design and effectiveness of organ donor registries; (iii) design and award in response to FY1999 appropriation of the first federal research grant program to develop model interventions for activities to increase donation; (iv) enactment of the Organ Donor Leave Act to increase leave for living donation from 7 to 30 days; and (v) implementation of provisions in the revised Hospital Conditions of Participation by HCFA requiring Medicare and Medicaid hospitals to report of deaths and imminent deaths to improve identification of potential donors.

- **Louisiana Organ Procurement Donor Registry Program.** NIAID is supporting the development, implementation, and evaluation of a statewide donor registry in Louisiana. Coupled with extensive school-, community-, and media-based educational programs, this registry aims to improve the rate of donation, especially among the state’s African-American population. This effort has resulted in an increase in donor registrations by 13% in two years. The registry, administered by the Department of Motor Vehicles, is available 24 hours a day, 365 days a year to maximize identification of potential organ donors.

- **Community-based Plan to Increase Minority Organ Donation.** NIAID supports a Demonstration and Education Outreach Project at the University of Washington to evaluate the effectiveness of a unique, community-based outreach network to increase knowledge of

and willingness to donate among Asian and African-American populations in Seattle and Tacoma, Washington. These researchers are also using culturally sensitive educational materials and community health education programs to increase donation awareness among Alaskan Natives.

- **National Minority Organ and Tissue and Transplant Education Program.** The NIH Office of Research on Minority Health, with the support of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) sponsors the National Minority Organ and Tissue Transplant Education Program (MOTTEP), to educate minority communities nationwide on issues concerning organ donation and transplantation. Minority populations are disproportionately in need of kidney transplantation due to the high incidence of renal disease. MOTTEP also directs an intensive campaign to reduce renal disease through education.

- **Bone Marrow Transplant Registries.** NIAID, the National Cancer Institute (NCI), and the National Heart, Lung, and Blood Institute (NHLBI) support the International Bone Marrow Transplant Registry (IBMTR) and the Autologous Blood and Marrow Transplant Registry (ABMTR). The IBMTR is an international study group engaged in the investigation of bone marrow transplantation for over 20 years and has collected data on bone marrow and/or blood cells from over 290 institutions worldwide. The diseases currently under study by these two resources include acute and chronic leukemia, Hodgkin's and non-Hodgkin's lymphomas, multiple myeloma, and breast cancer. Studies also address questions regarding short- and long-term outcomes in defined patient groups, relevant prognostic factors, the efficacy of different transplant approaches, and the economic impact of BMT. Both registries contain information on over 57,000 BMT recipients, provide essential data for monitoring the efficacy of BMT, and are a national resource for patients and patient advocacy groups, physicians, researchers, Congress and NIH.

- **Diverse National Unrelated Umbilical Cord Blood Bank.** This program will determine whether stem and progenitor cells from umbilical cord blood are a clinically acceptable alternative to those from bone marrow or peripheral blood in unrelated donor transplants. NHLBI supports this program as part of the **Cord Blood Transplantation Study**.

- **Post-Transplant Tumor Registry.** Post-transplantation lymphoproliferative disorders (PTLD) is a heterogeneous grouping of lymphoid malignancies that can occur months to years after solid organ transplantation. To date, the University of Cincinnati has maintained the international PTLD database. However, through the efforts of the NIAID and the American Cancer Society, this database is being incorporated into the Scientific Registry of the Organ Procurement and Transplantation Network (OPTN). This database is an invaluable tool for the transplant community as it supplies not only incidence data on PTLD, but also important information relating immunosuppressive regimens to types, severity and incidence of PTLD. This information has led to a better understanding of the range of manifestations of PTLD and improved the diagnosis of this unusual disorder. The integration with the OPTN will ensure continued collection of this information to allow further studies to improve the quality-of-life for transplant recipients.

DEVELOPMENT OF NEW REAGENTS AND METHODOLOGIES FOR HISTOCOMPATIBILTY TESTING IN MINORITIES

For almost twenty years, NIAID has been associated with efforts to characterize, acquire, and distribute reagents defining the molecules involved in graft rejection. These efforts have progressed from the acquisition and distribution of reagents for standard HLA-typing to a focus on improving the definition of ethnically-restricted HLA genes and an initiative to identify the relevant organ-specific molecules involved in graft rejection.

The NIAID has supported a national program on the identification of HLA genes in African-American, Native American, and Hispanic populations since 1980. Specific accomplishments of this program include:

- Development of specific DNA reagents to further enhance HLA typing in minority populations.
- Definition of 13 new HLA genes in African-Americans, thereby reducing the number and frequency of incomplete tissue matching for these transplant recipients.
- Definition of 3 new HLA genes in Alaskan Yupik Eskimos, thereby reducing the number and frequency of incomplete tissue matching for these transplant recipients.

In addition, NCI, in cooperation with NIAID and NHLBI, continues its long-standing support of the International Histocompatibility Working Group (IHWG), which focuses on standardizing histocompatibility testing worldwide. These efforts develop highly sensitive techniques and reagents for HLA typing that ensure all recipients receive the best-matched donor organs available. Past accomplishments have led to significant advances in HLA typing, including:

- Development of the microcytotoxicity assay for HLA matching.
- Introduction of computers to HLA analysis, ensuring more accurate typing.
- Discovery of the mixed lymphocyte reaction (MLR) and antibodies to detect HLA types.
- Introduction of molecular methods to define HLA diversity at the genetic level.
- Association of HLA genes with specific diseases, including type I diabetes and celiac disease.

The 13th IHWG in 2000-2005 will extend these previous advances and further define HLA diversity at the molecular level by establishing DNA-based technologies as the standard for HLA typing. Topics that will be explored by the 13th IHWG include:

- **HLA Expression in Cancer.** Abnormalities in HLA gene expression in malignant cells appear to play a role in the clinical course of the disease and to counteract T cell-based immunotherapy. This project will contribute to a better understanding of the pathogenesis of these diseases and will likely have a positive effect on immunotherapy.
- **Genetic Map of Minor Histocompatibility Antigens.** Minor Histocompatibility Antigens (mHA), i.e. non-HLA genes involved in graft rejection, may cause graft failure in HLA-matched transplants. These studies will define mHA involvement in solid organ, tissue and cellular graft rejection.

- **The Anthropology/Human Diversity Project.** This project will use DNA-based techniques to study HLA diversity in a large number of geographically and ethnically distinct human populations. The resulting database will accelerate the association and analysis of HLA genes with specific diseases.
- **HLA Genes and Diseases.** This project will identify candidate genes in the HLA complex that influence the risk of disease. Identifying such genes will allow physicians to develop health care strategies long before disease onset. Five diseases, for which the primary HLA associations have been well established, are: type 1 diabetes (IDDM), celiac disease (CD), ankylosing spondylitis (AS), rheumatoid arthritis (RA) and narcolepsy (NC).
- **Donor Registry Typing Project and Bioinformatics for HLA Diversity Analysis.** Standardization of HLA typing methods, reagents, and data reporting is necessary to minimize ambiguous matching, avoid inadvertent exclusion of potential matches, and improve the overall efficiency of the donor search process. New HLA variants will be identified, as large numbers of volunteer donors are typed. The HLA diversity of donor repositories will be helpful in guiding donor searches and deciding future strategies for donor recruitment. The long-term goal of this project is to establish a system that will sustain the HLA sequence database and the typing tools to serve as a research and clinical resource.

IMMUNOSUPPRESSION AND IMMUNE TOLERANCE

Proper regulation of the immune system is of paramount interest in transplantation immunology. Whereas the development of immunosuppressive drugs has been greatly successful in improving short-term graft outcomes, side effects and associated risks require continued work in this area. NIH supports and coordinates many clinical trials designed to optimize current therapies and develop new protocols in combination therapies. The ultimate goal of transplantation immunology however, is the induction of **donor-specific tolerance**, *i.e.* the ability to turn off only that component of the recipient's immune response that is directed toward the transplanted organ, tissue, or cells. NIH has made immune tolerance a major priority and has developed a broad-based, long-range plan to accelerate research in this important area. Major features of the plan include:

- Integrating underlying mechanistic studies into non-human primate and clinical research.
- Facilitating partnerships with the pharmaceutical and biotechnology industries by creating infrastructures that will accelerate quality pre-clinical and clinical research.
- Investing in basic research to define the molecular basis of tolerance induction and maintenance to expand the approaches to tolerance induction.

Basic Immunology. Because the immune system is the greatest barrier to successful transplantation, continued investment in basic immunology research is fundamental to ensuring progress in transplantation. Additionally, advancements in basic immunology will influence the fields of vaccine development, autoimmunity, asthma and allergic diseases and cancer immunotherapy. NIH has developed the following solicited research program to address salient questions in the basic immunology of humans.

- **Human Immunology Centers of Excellence.** Human studies are limited by a more restricted set of experimental protocols than can be performed in animals. Extensive genetic and environmental diversity further complicate the ability to obtain detailed information about the processes that govern immune responses. The goal of this NIAID initiative is to support highly integrated, multidisciplinary research programs to define the mechanisms responsible for normal or pathogenic human immune responses.

Immune Tolerance. The successful induction of immune tolerance is a major goal for the treatment of many immune-mediated disorders, including graft rejection, autoimmune diseases, and asthma and allergic diseases. Advances in tolerance induction would provide valuable new therapeutic strategies that do not require life-long, globally immunosuppressive therapy. NIH-supported researchers have defined many of the cellular pathways leading to the activation of T cells. These events are necessary for immune responses against pathogens and tumors but also lead to graft rejection and autoimmune diseases. By elucidating these immunological events, researchers are identifying new targets for immunosuppressive or tolerogenic therapies. Some of these basic processes are:

- T-cell recognition of incompatible donor HLA molecules on the graft. This constitutes the first signal for antigen-specific activation of T cells. Unfortunately, interruption of this step not only prevents the response to the graft, but also responses to viruses, bacteria, and tumors, thereby leaving the patient susceptible to these threats.
- T-cell costimulatory signals. Along with recognition of HLA molecules, costimulatory signals are necessary for T cell activation. This is an exciting area of research because blockade of costimulatory signals may induce donor-specific tolerance. Strategies to block this signal **(costimulation blockade)** in animal models of transplantation have been promising, and clinical trials are underway to test these strategies in humans.
- Cellular signaling pathways. Elucidation of the biochemical events that immediately follow recognition of HLA molecules by T cells has identified targets for drug therapy. Examples of drugs that target these pathways and are currently used in transplantation are: Cyclosporine, Tacrolimus, and Sirolimus.
- Metabolic pathways. Cell growth and division are prime targets for immunosuppressive therapy. The identification of biochemical components involved in these processes has generated targets for therapeutic drugs in transplantation and autoimmune diseases, and has led to breakthrough therapies for immunodeficiency diseases that mainly affect children.
- Cytokines. These protein messengers of the immune response can be classified by their abilities to induce or inhibit inflammatory responses. Biological agents are being developed to inhibit the cytokines that promote graft rejection.

Through the research programs listed below, NIH has established cooperative efforts among researchers in the United States and elsewhere to aggressively pursue tolerance induction protocols in pre-clinical and clinical studies.

- **Immune Tolerance Network.** To facilitate and accelerate the clinical application of promising tolerance-induction strategies, NIAID, with co-sponsorship from NIDDK and the Juvenile Diabetes Foundation International (JDFI), recently established the Immune

Tolerance Network. This unique, multi-institutional consortium unites more than 70 researchers and clinicians from 40 institutions to evaluate the safety and efficacy of tolerance induction protocols in kidney and islet transplantation, autoimmune diseases, and asthma and allergic diseases.

- **Non-Human Primate Transplant Tolerance Cooperative Study Group.** In this solicited research program from NIAID, NIDDK, and the National Center for Research Resources (NCRR), investigators are evaluating new strategies to induce **donor-specific tolerance** in pre-clinical transplantation settings. Information on the safety and efficacy of these strategies will be necessary before the Immune Tolerance Network can apply them and other NIH-sponsored clinical trials of transplant tolerance.

- **Innovative Grants on Immune Tolerance.** The goal of this NIAID initiative is to support innovative basic projects on immune tolerance and to encourage young investigators working in other areas of research to bring novel perspectives and expertise to this field. High risk, high impact projects are sought that have the potential to significantly increase our understanding of the mechanisms that induce long-lived immune tolerance.

- **Autoimmunity Centers of Excellence.** This multi-institute cooperative program focuses on pilot clinical trials of promising tolerogenic and immunomodulatory approaches to treat multiple autoimmune diseases such as rheumatoid arthritis, type 1 diabetes and multiple sclerosis. This research centers program will integrate basic and clinical research to evaluate the safety, potential efficacy, and underlying mechanisms of tolerogenic treatment strategies.

- **NIH Director's 1% Transfer Authority Funds.** In FY 1998, NIAID received $4.5 million from the NIH Director's 1% Transfer Authority Funds. These funds supported cooperative research agreements to evaluate tolerance-induction protocols in non-human primate models of kidney and islet transplantation. Results from these programs will guide protocol development in the **Immune Tolerance Network**. These funds also supported a Program Project Grant to address basic mechanisms of immune tolerance that will be applicable to graft rejection, autoimmune diseases, and asthma and allergic diseases.

- **Ethical Issues in Immune Tolerance.** A major ethical dilemma in the induction of transplant tolerance results from the knowledge that standard immunosuppressive therapy prevents the induction of at least some types of tolerance. Therefore, to evaluate the safety and efficacy of tolerogenic approaches to transplantation, clinical trials will involve withholding standard therapy or significantly altering immunosuppressive regimens. In April 1998, NIAID convened an expert panel to begin developing guidelines for the design, conduct, and monitoring of scientifically and ethically acceptable clinical trials to evaluate the safety and efficacy of new approaches to achieve immune tolerance in transplant recipients. A group of experts in bioethics, law, and basic and clinical research joined NIH staff and representatives of the Food and Drug Administration and the NIH Office of Protection from Research Risks. Their recommendations can be viewed on the World Wide Web at http://www.niaid.nih.gov/publications/immune/CONTENTS.HTM

Immunosuppressive Therapies. Drug discovery has taken advantage of *in vitro* assay systems for immune activation to screen compounds for their immunosuppressive potential. These assays, such as MLR and cytotoxicity testing, were developed through research into basic immune mechanisms. Many of these mechanisms have been identified through NIH-supported basic research programs. Discoveries in these areas have been the impetus for both established pharmaceutical companies and emerging biotechnology companies to develop therapeutic agents that inhibit unwanted immune responses in transplantation and autoimmune diseases (Appendices C and D). In addition, NIH has facilitated the development of new therapeutic agents and assay systems through Cooperative Research and Development Agreements (CRADAs) with private industry.

The development of immunosuppressive agents, such as cytotoxic drugs, corticosteroids, and calcineurin inhibitors, has increased the one-year survival rate of grafts. However, in addition to increasing risks of infection and malignancy, long-term use of these agents is associated with serious side effects, such as kidney damage, joint problems, and hypertension.

Reducing these complications, while improving graft survival, is a priority in transplantation immunology. For many years, NIH has supported basic research in immunology, pre-clinical testing of new therapeutic regimens, and cooperative clinical trials to improve short- and long-term graft survival in transplant recipients. Research is currently focused on developing biological modifiers of T-cell activation. The advantages of biological approaches include the potential to: i) emulate natural regulatory pathways in the immune system; ii) induce donor-specific tolerance; iii) eliminate or reduce the need for life-long therapy; and iv) lower the risk of cumulative toxic effects. Recent accomplishments in tolerance and immunosuppression include the following:

- Induction of stable allograft tolerance with the combination of Rapamycin and costimulation blockade (Dr. Terry Strom, Harvard Medical School; and Dr. Laurence Turka, University of Pennsylvania).
- Prevention of GVHD in children undergoing BMT for leukemia. (Drs. Lee Nadler and Eva Guinan, Dana Farber Cancer Institute).
- Induction of tolerance in a mouse model of skin grafts with costimulation blockade and bone marrow transplantation (Dr. Megan Sykes, Massachusetts General Hospital).
- Inhibition of GVHD in a mouse model with costimulation blockade (Dr. Bruce Blazar, University of Minnesota).

KIDNEY TRANSPLANTATION

Kidney disease is a severe and costly public health problem that is increasing in the U.S. An estimated 10.9 million Americans suffer from kidney disease, including more than 360,000 who depend on dialysis or a kidney transplant to survive. The costs of treating end-stage renal disease (ESRD) under the federal Medicare program are now estimated at approximately $15 billion annually, with Medicare paying $11.8 billion. Kidney transplantation ultimately provides a better quality of life and reduced medical expenses, when compared to a lifetime of dialysis

treatments[7]. Kidney transplantation accounts for 57% of all transplant procedures. This reflects the fact that many common diseases, including diabetes and glomerulonephritis (a heterogeneous group of immunological diseases), result in ESRD, for which transplantation is the preferred treatment. In addition, the kidney donor pool is larger than that of other organs as both living and cadaveric donors may provide kidneys.

NIH supported research efforts in ESRD and kidney transplantation include:

- **NIH Intramural Kidney and Islet Transplantation Program.** Researchers from the National Naval Medical Center, the Walter Reed Army Medical Center, NIDDK, and the NIH Clinical Center have established a program to conduct clinical trials in kidney, kidney-pancreas, and islet cell transplantation. The goal of the program is to develop methods that permit transplantation without the need for chronic immunosuppression or with a greatly reduced need for immunosuppression.

- **Cooperative Clinical Trial in Adult Transplantation.** NIAID launched the Cooperative Clinical Trial in Adult Transplantation (CCTAT) in FY1991 and renewed this program in FY1995 to establish and coordinate multi-center clinical trials of new immunosuppressive protocols in renal transplantation. This effort has led to significant changes in the standard-of-care for transplant recipients, and has enabled the clinical trials of new combination therapies not achievable outside the CCTAT network.

- **Cooperative Clinical Trials in Pediatric Transplantation.** Kidney transplantation in children presents unique challenges. It is more difficult to suppress the immune system of children than that of adults. Furthermore, children are more predisposed to graft rejection then adults and reject grafts more vigorously. Nevertheless, transplantation is the best therapy for children with ESRD, as it improves patient survival and reduces psychological, developmental, and growth problems. The Cooperative Clinical Trials in Pediatric Transplantation (CCTPT), launched by NIAID in FY1994 and renewed in FY1999, is developing clinical strategies to treat and prevent graft rejection specifically in children.

- **Banff Conference on Allograft Pathology.** NIAID co-sponsored BANFF 97 and 99, a biennial international meeting to establish criteria for the diagnosis of graft rejection. This meeting incorporated new knowledge from the NIAID-supported CCTAT and CCTPT to revise the criteria for diagnosis of kidney graft rejections. The resulting modifications have a significantly influenced the standard-of-care kidney transplant recipients receive during a rejection episode.

- **U.S. Renal Data System.** The United States Renal Data System (USRDS) collects and analyzes information on the incidence, prevalence, treatment, morbidity, and mortality of ESRD in the United States. The USRDS is operated by the University of Minnesota, and is funded primarily by NIDDK, with supplementary funding from HCFA. The USRDS is a valuable source of information on renal transplants performed through Medicare reimbursement.

[7] Wolfe, R. A., et al. 1999. Comparison of Mortality in all Patients on Dialysis, Patients on Dialysis Awaiting Transplantation, and Recipients of a First Cadaveric Transplant. *New England Journal of Medicine*. 341:1725-30.

- **Clinical Trial of Tolerance Induction in Adult Kidney Transplantation.** In 1999, NIAID, in collaboration with Biogen, began phase I/II clinical trials on the use of anti-CD40L, an inhibitor of T cell costimulation, to induce immune tolerance in adult kidney transplantation. Although this reagent yielded promising results in pre-clinical studies, adverse events have temporarily halted patient enrollment in the trials. However, valuable clinical samples were obtained from the trials for studies into the mechanisms of action of anti-CD40L and graft rejection.

Further clinical accomplishments in kidney transplantation include:

- Induction of stable immune tolerance to a kidney graft in combination with bone-marrow transplantation (Dr. Thomas Spitzer and Dr. Benedict Cosimi, Massachusetts General Hospital).
- Prevention of hyperacute rejection with Intravenous Immunoglobulin (Dr. Stanley Jordan, Cedars-Sinai Medical Center).
- Demonstration that kidney biopsies do not contribute to rejection and can be used to safely detect and facilitate early treatment of rejection episodes in pediatric transplant recipients (Cooperative Clinical Trials in Pediatric Kidney Transplantation)
- Potential to improve outcomes in kidney transplants between HLA-nonidentical siblings by using maternal HLA-typing (Dr. William Burlingham, University of Wisconsin, and Dr. Michael Bean, Dendreon Corporation).
- Induction of long-term, donor-specific tolerance by costimulation blockade in a nonhuman primate model of renal transplantation (Dr. Allan Kirk, National Naval Medical Center, and Dr. David Harlan, National Institute of Diabetes, Digestive, and Kidney Disorders).

LIVER TRANSPLANTATION

Liver malfunction can result from several organ-damaging conditions such as viral or alcoholic hepatitis, alcohol-related cirrhosis and biliary atresia. NIH promotes the goals and objectives necessary to enhance knowledge regarding liver and biliary disease, including liver transplantation. NIDDK has encouraged research in such areas as prevention of recurrent disease after liver transplantation and implications of alcohol, hormones, and medical complications in liver transplantation. The major research goals related to liver transplantation are to:

- Improve methods in collection and preservation of functional livers.
- Develop and validate models to predict mortality/morbidity and recurrence of complications.
- Improve the management of infectious and medical complications and recurrence of liver disease post transplantation.
- Develop the areas of hepatocyte transplantation, hepatic gene therapies, and bioartificial liver support devices.

Accomplishments of NIH programs in liver transplantation include:

- **Accessibility of Liver Transplantation Data.** The NIDDK supported a long-term study on outcomes of liver transplantation that addressed important issues including the management of patients with liver disease. The database was constructed from information gathered on all patients undergoing liver transplantation at three large U.S. liver transplant centers. The database is accessible to the scientific community.

- **New Surgical Techniques in Liver Transplantation.** To increase the number of liver transplants with the available donor pool, transplant surgeons are assessing the benefits and risks of split liver transplants versus living donor transplants. The split liver technique allows the donated cadaveric liver to be divided into two parts that can be transplanted in different patients. Although split liver transplants are currently the preferred procedure, few liver transplant centers in the U.S. perform them.

- **Bioartificial liver.** The General Clinical Research Center at Cedar Sinai Medical Center has a long-standing program, supported by NCRR, to develop an artificial liver that can provide temporary physiological support for a failing liver or serve as a bridge to maintain patients with end-stage liver disease while they await a donor liver for transplantation.

PANCREAS AND ISLET CELL TRANSPLANTATION

Type 1 diabetes affects up to 1.6 million Americans, and is the leading cause of pancreas failure due to the deterioration of insulin-producing islet cells. Because diabetes also leads to ESRD, patients may receive pancreas, kidney, or combined kidney-pancreas transplants. One of the Immune Tolerance Network's areas of initial focus will be the development and assessment of tolerance induction protocols in islet cell transplantation.

Transplantation of the insulin-producing islets of the pancreas has been proposed as an alternative to whole pancreas transplants because of reduced surgical risk. However, the one-year success rate of islet transplantation for type 1 diabetes in humans (defined as independence from insulin therapy) is in the range of 5% to 10%. A contributing factor to this poor success rate is the reoccurrence of the autoimmune destruction of the transplanted islets. Thus, successful transplantation protocols should prevent both graft rejection and reoccurrence of autoimmune disease. Recent studies in non-human primates have demonstrated that ablation of T cells can prevent islet-graft rejection and symptoms of diabetes up to two years post-transplant (Dr. Judith Thomas, University of Alabama – Birmingham). Successful islet transplantation in humans will draw on results from pre-clinical studies, including the **Non-Human Primate Transplant Tolerance Cooperative Study Group**. The collective aim of these studies is to make successful islet transplantation a reality by:

- Developing more effective and less toxic drugs and tolerogenic approaches to block immune destruction of islets.
- Improving methods to harvest and maintain cadaveric islets prior to transplantation.
- Assessing strategies for developing alternatives to human islets obtained from autopsy, such as genetically engineered surrogate beta cells or human beta cell lines.

- Developing techniques to protect islets or beta cells from immune rejection, either by encapsulation procedures or by genetic engineering.

Additional programs supported by NIDDK to develop pancreas and islet transplantation include:

- **Pancreas Transplant Registry.** This registry coordinates activities with the United Network of Organ Sharing (UNOS) to collect basic data on U.S. pancreas transplant cases. As of July 1998, the registry had collected data on 9,943 pancreas transplants from 237 institutions.

- **Human Islet Transplantation into Humans.** This joint NIDDK/JDFI program will support studies leading to and evaluating new treatment regimens for islet transplantation.

HEART TRANSPLANTATION

A number of cardiac diseases result in heart failure, for which cardiac transplantation is the only successful treatment. The primary indications for heart transplantation are coronary artery disease and cardiomyopathy in adults, and congenital heart disease in children. Nearly 5 million people in the United States have some form of heart failure and 20,000 to 40,000 of these could benefit from a heart transplant. However, organ shortages prevent 90% of these patients from receiving a transplant. In patients who survive the first year after transplant, chronic rejection is the major cause of death. While ESRD patients can be kept alive on dialysis and diabetics can take insulin, heart failure patients have no such "safety net." Thus there is a critical need to find alternatives to human organs for transplantation. These include xenotransplantation, cell transplantation, and mechanical assist devices.

Accomplishments in heart transplantation include:

- Development of a non-invasive, breath-analysis method to detect cardiac rejection (Dr. Michael Phillips, Menssana Research, Inc.).
- Inhibition of immune-mediated damage by gene therapy in a mouse model of cardiac transplantation (Dr. Richard Simmons, University of Pittsburgh.).
- Reduction of chronic rejection with cobalt protoporphyrin in an animal model of cardiac transplantation (Dr. Charles Orosz, Ohio State University).
- Identification of the inflammatory mediators of chronic rejection in animal models of cardiac transplantation (Dr. Peter Libby, Brigham and Women's Hospital; Dr. Jordan Pober, Yale University; Dr. Fred Sanfilippo, Johns Hopkins University).

LUNG TRANSPLANTATION

Lung transplantation is a viable therapy for patients with a variety of end-stage lung diseases, including emphysema and cystic fibrosis (CF), and has shown continued growth since the first successful procedures in the early 1980s. The age distribution for lung transplantation is younger than for heart or heart-lung transplant recipients primarily due to its use in the CF

populations. Research into the use of reduced-size adult lung transplants for the pediatric population is ongoing. Another major focus of research is to design strategies to prevent acute and chronic graft dysfunction and to prevent the development of post transplant infections. Lung transplantation remains a developing field within pulmonary medicine and ongoing clinical and basic research should continue to advance the field and ultimately lead to more acceptable long-term outcomes for lung transplant recipients. Accomplishments in clinical lung transplantation and pre-clinical research include:

- Reduction of acute rejection with anti-thymocyte induction therapy (Dr. Duane Davis, Duke University).
- Regulation of the P-glycoprotein membrane pump involved in modulating organ rejection by altering access of immunosuppressive drugs into cells (Dr. Gilbert Burckhart, University of Pittsburgh).
- Inhibition of acute rejection by local delivery of aerosolized cyclosporine therapy in a rat model (Dr. Bartley Griffith, University of Pittsburgh).
- Reductions in lung reperfusion injury by interrupting inflammatory pathways following transplantation in a rabbit lung model (Dr. Irving Kron, University of Virginia-Charlottesville).
- Achievement of stable pulmonary function after transplantation of a mature lobar graft in a porcine model (Dr. Irving Kron, University of Virginia-Charlottesville).
- Reduction of ischemia-reperfusion injury and rejection by gene transfer into rat lung grafts (Dr. G. A. Patterson, Washington University-St. Louis).
- Identification of specific immune-deficiencies associated with chronic cytomegalovirus (CMV) infection after lung transplantation (Dr. Adriana Zeevi, University of Pittsburgh).

BONE MARROW AND STEM CELL TRANSPLANTATION

More than 20,000 bone marrow and stem cell transplants were performed in 1998 to restore hematopoietic cells (the source of mature blood cells) that are destroyed by radiation or chemotherapy, or to correct genetic defects of the hematopoietic system. Bone marrow transplantation (BMT) is used to treat non-malignant diseases such as aplastic anemia and beta-thalassemia, and several forms of cancer including: breast cancer, Hodgkin's and non-Hodgkin's lymphoma, multiple myeloma, chronic myeloid leukemia, acute myeloid leukemia, and acute lymphoblastic leukemia. Patients who receive transplants for leukemia or severe aplastic anemia and remain disease-free at two years post transplant have an 89% probability of living at least 5 years longer. It is estimated that 30,000-40,000 persons are alive now more than 5 years after BMT.

The success of BMT is limited by potentially fatal complications such as interstitial pneumonitis, cytomegalovirus (CMV) infection and GVHD. Currently, NIH sponsors several programs that explore the causes of post-BMT complications, alternatives to standard BMT procedures, and alternative therapeutic uses of BMT. These programs include:

- **Mechanisms of Post Bone Marrow Transplantation Lung Injury.** In FY1995, NHLBI launched this program to promote research into the contributing factors of post lung

transplant lung injury including interstitial pneumonitis, which contributes to 40 percent of deaths related to BMT.

- **Vaccine Development for Cytomegalovirus Infection.** Ganciclovir has reduced post-BMT mortality due to HCMV infections. However, side effects of Ganciclovir therapy limit its effectiveness. Therefore the NIH supports research into vaccines and improved therapies against HCMV.

- **Unrelated Donor Transplant Trial of T-Cell Depletion for the Prevention of GVHD.** This program, begun in FY1993 by NHLBI, supports the development of new procedures to understand and ultimately inhibit GVHD.

- **Cord Blood Transplantation Study**. Using umbilical cord blood as a source of stem cells, the incidence of GVHD is reduced even when the donor and recipient are not HLA matched. NHLBI supports the Cord Blood Transplantation Study (COBLT), a national study to address the use of umbilical cord blood in transplantation. Another important goal of this study is to build a cord blood bank from ethnically diverse donors.

- **Stem Cell Transplantation for the Treatment of Autoimmune Diseases.** Animal studies and early clinical evidence suggest that bone marrow stem cell transplantation may promote the remission of autoimmune diseases. This contract, supported by multiple institutes, will investigate the mechanisms by which BMT alleviates autoimmunity.

Accomplishments of research in bone marrow and stem cell transplantation include:

- Prevention of GVHD by *ex vivo* treatment of bone marrow with costimulation blockade (Dr. Lee Nadler, Dana Farber Cancer Institute).
- Identification of inflammatory mediators and metabolic defects that lead to lung damage after transplantation (Dr. James Ferrara, University of Michigan; Dr. Brian Christman, Vanderbilt University).
- Use of novel regimens for marrow transplantation in humans based on results from a canine model (Dr. Rainer Storb, Fred Hutchinson Cancer Research Center).
- Establishment of a mouse model of bone marrow post-transplant lung injury for the development of therapies for patients (Dr. Bruce Blazar, University of Minnesota).
- Accelerating the regeneration of immunity after BMT in a mouse model (Dr. Ken Weinberg, Los Angeles Children's Hospital).

OCULAR TISSUE TRANSPLANTATION

Approximately 13 million Americans are either legally blind, or have visual impairments that cannot be corrected and millions more have potentially blinding eye diseases. Damage to two areas of the eye, the cornea and the retina, may be treated by transplantation.

Corneal Transplantation. Over 45,000 corneal transplants were performed in 1998 to treat corneal blindness resulting from a variety of diseases, injury, and infection. Corneal

transplantation has a greater than 90% success rate. This is in part because the cornea is an immunoprivileged site, i.e., an anatomical location that is protected from routine immune surveillance due to lack of circulation and/or to the presence of immuno-inhibitory molecules. The Corneal Diseases Program at the National Eye Institute (NEI) supports research that focuses on improving the efficacy of transplantation and reducing the risk of rejection.

Retinal Transplantation. Under NEI's Retinal Diseases Program, the feasibility of transplanting retinal tissue to restore sight for those people suffering from retinal diseases is being investigated in animal models. Early results from these studies demonstrate that retinal tissue can be transplanted in the eyes of experimental animals.

CHRONIC REJECTION

While advances in the past five years have dramatically increased the one-year survival rate of grafts, long-term graft survival has not changed. **Program Projects in the Immunopathogenesis of Chronic Graft Rejection**, a joint venture of NIAID and NHLBI, was launched in 1996 and will be renewed in 2001 to enhance our knowledge of the mechanisms of chronic graft dysfunction. To accomplish this, further research in humans is needed to:

- Define the non-immunological factors leading to immune-mediated damage.
- Determine the role of sub-clinical rejection in pathogenesis of chronic rejection.
- Determine the role of chronic infections (cytomegalovirus, hepatitis, respiratory syncytial virus, and Epstein Barr virus) in the pathogenesis of chronic rejection.
- Delineate the role of the above during identified phases of chronic rejection.
- Understand the immune response to injury, including immune recognition and activation, effector functions leading to inflammation, and regulatory functions leading to fibrosis.

Already, researchers have identified some of the contributing factors in chronic graft rejection, including:

- Correlation of cytomegalovirus (CMV) infection with the onset of chronic graft dysfunction (Dr. Charles Orosz, Ohio State University).
- Demonstration of T cell involvement in chronic rejection of cardiac grafts (Dr. Chris Platsoucas, Temple University).
- Identification of mediators of organ injury that increase the risk of chronic rejection (Dr. Nicolas Tilney, Brigham and Women's Hospital).

XENOTRANSPLANTATION

A major factor in the increasingly long waiting lists for organs is the unavailability of donors. The severe shortage of human organs suitable for transplantation has renewed interest in the potential use of organs obtained from other species. An analysis of possible animal organ sources in xenotransplantation has concluded that pigs are the best choice based on anatomical and physiological similarities to humans, and the ease of breeding large herds. However, this

approach has serious limitations, including: i) histocompatibility barriers between species; ii) the possibility of delayed acute vascular xenograft rejection; and iii) the inability to identify, quantify, and minimize the risks of transmitting infectious agents to xenotransplant recipients and the general public.

The Institute of Medicine (IOM) of the National Academy of Sciences held a three-day workshop in June 1995 to discuss xenotransplantation. From the meeting, the IOM panel concluded that:

- National guidelines must be developed and required of all experimenters and institutions that undertake xenotransplantation trials.
- Further investigation is necessary into the ethical issues raised by xenotransplantation, including informed consent and the fairness of organ allocation.
- A mechanism should be established within DHHS to coordinate federal endeavors in xenotransplantation and to ensure proper development, oversight and evaluation of established guidelines.
- Well-chosen human xenotransplantation trials would be justified and should proceed when the scientific knowledge for specific types of xenotransplants is judged sufficient and appropriate safeguards are in place.
- Special caution is required to ensure proper source animal screening and post-transplantation monitoring to ensure the public's safety from infectious agent transmission.

To address the issue of infectious agent transmission in xenotransplantation, NIH hosted the **Cross-Species Infectivity and Pathogenesis Meeting** in July 1997. The consensus of this meeting was that the transmission of infectious agents to the xenograft recipient was indeed a potential risk, but the threat of transmitting such an infection to the general population was small. It was suggested that breeds of pigs that are free of infectious agents should be developed to reduce these risks. As a result of this meeting, NIAID, NIDDK, and NHLBI issued a request for applications to conduct research on the immune response to xenotransplants and xeno-infectious agents.

An improved understanding of the immune recognition and rejection of xenografts has resulted in new therapies that can partially overcome hyperacute rejection, delayed xenograft rejection, or acute vascular xenograft rejection. The final therapeutic regimen that will allow survival of a discordant xenograft is likely to involve a combination of 'modified' functional genes in the donor organ, the development of immunological tolerance to pig antigens and administration of novel therapeutic agents that can control the immune responses to xenografts. Studies are underway to further define the immune response to non-human antigens and assess cross-species infectivity in xenotransplantation. The NIH and NIAID are seizing the opportunity to support these endeavors, including:

- Identifying the targets for and mediators of human responses against xenografts.
- Inhibiting recipient immune responses to xenografts by inducing tolerance or removing specific immune system components (e.g. antibodies that precipitate hyperacute rejection)

- Genetically manipulating donor animals or tissues by insertion of transgenes that enhance resistance to immune responses.
- Developing novel immunosuppressants that control the recipient's natural killer cell- and monocyte-mediated immune responses
- Assessing the probability of viral recombination in xenotransplant recipients, leading to a new, pathogenic virus.
- Assessing the risk of transmission of xenozoonoses (cross-species infectious diseases), and developing new diagnostic methods to detect xenozoonoses before they become established infections.
- Evaluating the *in vivo* safety and efficacy of antimicrobial therapeutics and their impact on the pathogenicity, infectivity, and transmissibility of xeno-infectious organisms.

NIAID represents NIH scientific interests in xenotransplantation through membership on the DHHS Xenotransplantation Working Committee. In the proposed **PHS Guideline on Infectious Disease Issues in Xenotransplantation,** this committee recommended establishment of an oversight committee to review Xenotransplantation protocols. The Secretary of Health and Human Services chartered the **Secretary's Advisory Committee on Xenotransplantation (SACX)** in July 1999 to consider the full range of complex scientific, medical, social, and ethical issues and the public health concerns raised by xenotransplantation, and to make recommendations to the Secretary on policy and procedures.

III. OPPORTUNITIES IN TRANSPLANTATION

In the 21st century, there will be many opportunities to extend transplantation to treat a wider range of diseases. As the American population ages and life expectancy increases, the number and types of transplantation procedures will also increase. NIH is committed to developing new therapeutic approaches to prevent graft rejection and expanding knowledge of the mechanisms of immune rejection. The coordination of research programs at NIH provides a broad basis for scientific leadership and funding opportunities among diverse diseases and organ systems. For a comprehensive summary of strategic plans from the collaborating institutes, please see the individual World Wide Web sites for details (e.g. http://www.niaid.nih.gov/strategicplan). These plans pave the way for significant scientific and clinical advances in key areas, some of which are outlined below.

IMMUNE TOLERANCE

Successful tolerance induction and maintenance transplantation is being pursued through NIH-solicited and investigator-initiated research programs described previously. Tolerance induction is a major therapeutic goal for the three major disease-related aspects of modern immunology: autoimmunity, transplantation, and allergy/asthma. Furthermore, understanding the basic processes that control immune recognition will facilitate new approaches to augment host defenses and protective immunity, including the design of improved vaccines. In addition,

clinical applications for tolerance induction will improve preventive and therapeutic approaches, including gene transfer, for non-immunological diseases. Examples include: cancer, neurological disorders, diabetic retinopathy, end-stage organ disease (e.g., kidney, liver and pancreas), and heart disease. Thus, findings generated from this research will be highly relevant to many NIH components.

NOVEL DIAGNOSTIC TECHNOLOGIES FOR THE PREDICTION OF GRAFT REJECTION

Graft rejection is currently diagnosed by symptoms of organ failure and often is not diagnosed early enough to allow successful medical intervention. New technologies for early and rapid detection of the immunological events preceding rejection will enable physicians to predict both the onset and intensity of rejection episodes and to take the appropriate therapeutic measures prior to organ damage. Currently, NIH-funded research includes magnetic resonance imaging (MRI) to non-invasively monitor immunological events in the grafted organ, and gene-expression and microarray techniques to detect the immune mediators of rejection. The latter studies will use biopsy, blood, and urine samples from transplant recipients in the **Cooperative Clinical Trials in Adult and Pediatric Kidney Transplantation**. In the future, these research programs will be expanded to examine the non-invasive collection of samples, identify surrogate markers that predict rejection prior to organ injury, monitor disease activity and responses to therapy, and predict long-term outcomes. This will be accomplished through collaborations among investigators within the **Cooperative Clinical Trials in Adult and Pediatric Kidney Transplantation**, the **Immune Tolerance Network**, and the **Non-Human Primate Transplant Tolerance Cooperative Study Group**.

NEUROLOGICAL DISORDERS

President George Bush declared the 1990's "The Decade of the Brain," which reflected a commitment to research in neuroscience. This commitment has been productive, as scientists have uncovered the mechanisms of several neurodegenerative diseases. These discoveries have increased the therapeutic options for such diseases. Immediate opportunities in transplantation for neurological disorders exist for the treatment of Parkinson's disease and Spinal Cord Injury.

Parkinson's Disease. Existing therapies for Parkinson's disease do not arrest the ongoing neurodegeneration, and the effects of therapy often fade with time. Research on new approaches to treat Parkinson's disease has shown that transplantation of genetically engineered cells in the brain restores function and promotes the survival of damaged cells. Although the graft survival rate is currently low (5 to 20 percent), there are indications of long-term improvement and some graft recipients have remained clinically stable after discontinuing medications. To date, the most successful transplantation strategy has used fetal cells. However, there are ethical concerns related to this approach. More research is needed to develop alternatives to fetal cells including cultured cell lines, bioengineered cells, or xenotransplantation. Areas of future study also include the determination of the optimal location for grafts, the potential benefits of multiple transplants, and the improvement of surgical techniques to enhance graft survival.

Spinal Cord Injury. Each year, an estimated 10,000 new spinal cord injuries cause permanent disability. Over 200,000 Americans now live with the effects of such trauma, and the estimated yearly medical costs approach $10 billion. Exciting new research has shown that paralysis in rats can be reversed by transplantation of immature nerve cells, suggesting that paralysis in humans can be overcome by transplantation of nerve cells or stem cells that can differentiate into neural tissue.

EMERGING TECHNOLOGIES

Gene Transfer. The identification of anti-inflammatory genes raises the possibility of gene transfer to reduce the anti-graft immune response. It is likely that grafts will be genetically engineered prior to transplantation, minimizing the risks of transferring genes directly to patients. Transplantation can also be used as a vehicle for gene therapy. Individuals suffering from disorders that are due to defective genes could receive transplants of hematopoietic stem cells that have been genetically modified to contain the correct form of the gene. This approach can also be used to restore functions that are lost to disease, e.g. replacing insulin-producing cells in diabetic patients.

Stem Cells. Bone marrow has been the primary source of hematopoietic stem cells for transplantation. This may change, as a recent study has shown that peripheral-blood stem cells (PBSC) provided an advantage in treating certain high-risk hematological malignancies. This finding has increased the use of PBSC in transplantation. Apheresis, the procedure for collecting PBSC, is less invasive than procedures for collecting stem cells from bone marrow. Minimizing discomfort to donors will likely reduce the anxiety associated with donating stem cells and increase numbers of interested donors. Additionally, **The Cord Blood Transplantation Study** addresses the use of umbilical cord blood, as a source of stem cells, in transplantation.

Stem cells have the potential to differentiate not only into blood cells, but also into many tissues. NIH-supported researchers have generated mature liver cells from mesenchymal stem cells (MSC) in the bone marrow, and similar results have been found for muscle cells, bone, cartilage, brain, and blood. In children with osteogenesis imperfecta, which leads to abnormally fragile bones, MSC infusions temporarily accelerate growth and reduce fractures. Recent findings from other laboratories suggest that stem cell transplantation will be used to treat neurological disorders. These exciting results have opened the door for the use of stem cell transplantation to replace or assist failing organs.

Xenotransplantation: As further research develops approaches to circumvent the histocompatibility barrier, hyperacute rejection, and other obstacles to xenotransplantation, this area will likely reduce the problem of organ shortages. Research will also identify new ways in which xenotransplantation can be used to alleviate diseases.

Tissue Bioengineering. Advances in cell biology and stem cell research will enable scientists to grow organs in the laboratory, starting from only a few cells. For example, any cell could theoretically be “instructed” to develop into a liver, kidney, or pancreas under the appropriate conditions. This would eliminate many of the current obstacles to organ transplantation, such as donor-recipient mismatches and limited organ availability. Researchers have already generated

an artificial cornea *in vitro*, a first step in synthesizing tissue of transplantable quality. Development and applications of tissue bioengineering techniques in other areas would enable:

- A transplant patient to "donate" an organ to himself, starting with a non-diseased cell that could be grown into a full or partial organ.
- The elimination of immunosuppressants, as the transplant is not foreign to the recipient.
- The establishment of cell and tissue banks as sources of transplantable material, thereby reducing the dependency on donated organs.
- Reductions in transplant waiting lists.

ETHICS

While the science of transplantation continues to take great strides, it must not be overlooked that particular experimental therapies will raise ethical concerns among some members of the public. Although the scientific rationale for gene therapy, xenotransplantation, and stem cell research may be quite clear to researchers, these areas may be quite controversial to the public as a whole. Forums that will discuss the ethical, legal, and social issues in biomedical research will guide policy decisions in these areas. These forums include:

- The NIH Office of Biotechnology Activities
- The NIH Office for Protection from Research Risks
- The Secretary's Advisory Committee on Genetic Testing
- The Secretary's Advisory Committee on Xenotransplantation
- The President's National Bioethics Advisory Committee

Ongoing communication among scientists, physicians, educators, ethicists, theologians, elected officials and the public is essential to guide the future of transplantation and to ensure that America continues to invest judiciously and responsibly in biomedical research.

IV. CONCLUSIONS

Society's investment in biomedical research has yielded tremendous advances in the quality of life for Americans. But with each advance comes a new set of challenges. The challenges that face transplantation are: improvement of long-term graft success rates, the establishment of long-term graft tolerance without harsh immunosuppressive drugs, and the reduction of lengthy waiting lists. Research into the basic mechanisms of disease has shown that transplantation can be used to treat many more diseases than was previously thought possible. As scientists continue to unravel basic biological processes, transplantation will assume an even larger role in medicine. Researchers have established successful pre-clinical models in transplantation, and the NIH is poised to translate their successes into clinical trials.

Appendix A: NIH-Sponsored Initiatives in Transplantation

Initiative	Supporting Institute(s)[a] and Organizations	FYs	Total Awards (Dollars)
Program Projects on the Immunopathogenesis of Chronic Graft Rejection	NIAID, NHLBI	2002-2007	[b]20,000,000
Innovative Grants on Immune Tolerance	NIAID, NIDDK	2001-2004	[b]7,100,000
Collaborative Network for Clinical Research on Immune Tolerance	NIAID, NIDDK, JDFI	2000-2007	[b]144,000,000
Human Islet Transplantation into Humans	NIDDK, JDFI	2000-2004	[b]20,000,000
Stem Cell Transplantation for the Treatment of Autoimmune Diseases	NIAID, NHLBI, NICHD, NIDDK, NIDCR, ORWH	2000-2004	[b]2,000,000
Pilot Studies for New Therapies for Type I Diabetes and its Complications	NIDDK, NCRR, NEI, NHLBI, NIAID, NICHD, NIDCR	2000-2001	577,813
Hyperaccelerated Award/Mechanisms in Immune Disease Trials	NIAID, NIAMS, NIDDK, NHLBI, NINDS, ORWH	1999-2003	5,177,839
Stem Cell Transplantation to Establish Allochimerism	NHLBI, NIDDK	1999-2002	11,018,642
Cooperative Clinical Trial in Pediatric Renal Transplantation	NIAID	1999-2002	8,857,752
Mechanisms of the Immune Response to Xenotransplant Antigens	NIAID, NIDDK, NHLBI	1999-2002	7,166,597
13th International Histocompatibility Working Group	NCI, NIAID, NHLBI, NCBI	1999-2001	9,780,666
Clinical Cancer Therapy Research	NCI	1999-2001	719,103
Nonhuman Primate Transplant Tolerance Cooperative Study Group	NIAID, NCRR, NIDDK	1998-2003	20,392,940
Basic and Clinical Research on Immune Tolerance	NIAID, NHLBI, NIA, NICHD	1998-2003	10,291,233
Direct vs. Indirect Antigen Recognition in Allograft Survival	NIAID, NHLBI, NIDDK, NIAMS	1998-2003	5,048,184
Minor Histocompatibility Antigens in GVHD and Graft Rejection	NIAID, NHLBI, NCI, NIDDK	1998-2003	3,032,240
Studies on the Quality of Life of Transplants and Their Families	NINR	1998-2001	6,809,863
Bone Marrow Transplantation Trials	NHLBI, NIAID, NCI	1998-2001	6,501,062
Cellular and Molecular Approaches to Achieving Euglycemia	NIDDK, NCRR, NIAID, NICHD, NIA, CDC	1998-2000	11,641,500
Exploratory Grants for Correlative Laboratory Studies & Clinical Trials	NCI	1998-2000	443,140
Prevention of Recurrent Disease After Liver Transplantation	NIDDK, NIAAA, NIAID	1998-1999	462,044
Immune Tolerance for Kidney and Islet Transplantation	NIAID, OD	1998	4,500,000
Transplantation Tolerance	NIAID, JDFI	1997-2000	13,067,485
Small Grants for Therapeutic Clinical Trials of Malignancies	NCI	1997-2000	436,188
Mechanisms of Post Bone Marrow Transplant Lung Injury	NHLBI	1996-2002	8,045,589
Cooperative Clinical Trial in Adult Transplantation	NIAID	1996-2000	8,352,126
Immunopathogenesis of Chronic Graft Rejection	NIAID, NHLBI	1996-1999	7,903,618
Human Stem Cell Sources and Transplantation Biology	NHLBI, NIDDK	1996-1999	5,869,390

[a] See Appendix B for a further description. [b] Estimated total awards

Appendix B: NIH Institutes, Offices and Co-Sponsoring Organizations in Transplantation Research

NCI	National Cancer Institute
NCRR	National Center for Research Resources
NHLBI	National Heart Lung and Blood Institute
NIAAA	National Institute on Alcohol Abuse and Alcoholism
NIAID	National Institute of Allergy and Infectious Diseases
NIAMS	National Institute of Arthritis and Musculoskeletal and Skin Diseases
NICHD	National Institute of Child Health and Human Development
NIDCR	National Institute of Dental and Craniofacial Research
NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases
NINDS	National Institute of Neurological Disorders and Stroke
NINR	National Institute of Nursing Research
NLM	National Library of Medicine
OD	Office of the Director (NIH)
ORWH	Office for Research on Women's Health
CDC	Centers for Disease Control and Prevention
HCFA	Health Care Financing Administration
JDFI	Juvenile Diabetes Foundation International

Appendix C: FDA-Approved Drugs and Biologics for Transplantation and Autoimmune Diseases.

Approved Drug/Biologic	Mechanism of Action
Cyclosporine/Neoral/Sandimmune	Cytokine synthesis inhibitor
Tacrolimus	Cytokine synthesis inhibitor
Sirolimus	Cytokine action inhibitor
Basiliximab	Cytokine action inhibitor
Daclizumab	Cytokine action inhibitor
Azathioprine/Imuran	DNA synthesis inhibitor
Mycophenolate mofetil/CellCept	DNA synthesis inhibitor
Methotrexate/Abitrexate/Rheumatrex	DNA synthesis inhibitor
Cyclophosphamide/Cytoxan/Neosar	DNA synthesis inhibitor
Leflunomide/Arava	DNA synthesis inhibitor/ Cytokine action inhibitor
Leukine	Immune reconstitution in BMT
ALG	Anti-lymphocyte/endothelial cell biological agents.
OKT3	Anti-lymphocyte/endothelial cell biological agents.
Anti-CD34	Anti-lymphocyte/endothelial cell biological agents.
Prednisone	Multiple or unknown mechanisms of action
Deoxyspergualin	Multiple or unknown mechanisms of action

Lieberman, Ronald. Classification and Mechanism of Action of Therapeutic Agents Used in Transplantation. In Ronald Lieberman and Asoke Mukherjee (eds.), Principles of Drug Development in Transplantation and Autoimmunity. R. G. Landes, Austin, TX. 1996. p. 109.

Appendix D: Selected Experimental Drugs and Biologics for Transplantation and Autoimmune Diseases.

Experimental Drug/Biologic	Indication
8-Methoxsalen	Prevention of acute rejection of cardiac grafts
ABX-CBL	Prevention of autoimmune disease, GVHD, graft rejection, and inflammation
Allogen	Hematopoietic reconstitution in BMT
Anti-CD2 Mab	Treatment of GVHD
Anti-human CD2 MAb	Prophylaxis of organ rejection
Anti-thymocyte serum	Treatment of graft rejection in solid organ transplantation and BMT.
Enbrel	Rheumatoid Arthritis
Hepatitis B Immune globulin, IV	Prophylaxis of Hepatitis B reinfection in liver transplant patients
Imciromab Pentetate	Detection of early necrosis in cardiac transplants
Interleukin-1 antagonist	Prevention of GVHD
MEDI-500	T-cell inhibitor in graft rejection and GVHD
Oral Beclomethasone	Treatment of intestinal GVHD
Recombinant MAb 5C8	Costimulation blockade